

DMB

Display Date 1-15-03  
Publication Date 1-16-03  
Certifier G. Pressley

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**Food and Drug Administration**

**21 CFR Part 201**

**[Docket No. 80N-0280]**

**RIN 0910-AA01**

**Over-the-Counter Vaginal Contraceptive Drug Products Containing  
Nonoxynol 9; Required Labeling**

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Proposed rule.

---

**SUMMARY:** The Food and Drug Administration (FDA) is proposing new labeling warning statements for all over-the-counter (OTC) vaginal contraceptive drug products containing nonoxynol 9. These warning statements will advise consumers that vaginal contraceptives containing nonoxynol 9 do not protect against infection from the human immunodeficiency virus (HIV), the virus that causes acquired immunodeficiency syndrome (AIDS), or against getting other sexually transmitted diseases (STDs). The warnings will also advise consumers that frequent use of vaginal contraceptives containing nonoxynol 9 can increase vaginal irritation. Increased vaginal irritation from use of nonoxynol 9 may increase the possibility of transmission of the AIDS virus (HIV) and STDs from infected partners. The agency is requesting public comment on the proposed labeling statements and how such information could best be presented in labeling. This proposal is part of FDA's ongoing review of OTC drug products.

**DATES:** Submit written or electronic comments by [*insert date 90 days after date of publication in the Federal Register*]. Submit written or electronic comments on the agency's economic impact determination by [*insert date 90 days after date of publication in the Federal Register*]. Please see section IX of this document for the effective date of any final rule that may publish based on this proposal.

**ADDRESSES:** Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to <http://www.fda.gov/dockets/ecomments>.

**FOR FURTHER INFORMATION CONTACT:** Arlene Solbeck, Center for Drug Evaluation and Research (HFD-560), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-2222.

**SUPPLEMENTARY INFORMATION:**

**I. Background**

In the advance notice of proposed rulemaking (ANPRM) for OTC vaginal contraceptive drug products (45 FR 82014, December 12, 1980), the Advisory Review Panel on OTC Contraceptives and Other Vaginal Drug Products (the Panel) placed nonoxynol 9 in category I (safe and effective). However, the Panel concluded that the contraceptive effectiveness of active ingredients cannot be considered separately from the vehicle and recommended that FDA require in vitro testing to determine the spermicidal effectiveness of each final formulation before marketing. In the preamble to the Panel's report (45 FR 82014), the agency stated that in vitro testing alone is an inadequate measure of a vaginal contraceptive product's effectiveness in humans. The agency

explained that clinical trials of each product or final formulation may be the only certain predictor of its effectiveness in humans. The agency added that if clinical trials are necessary, manufacturers may be required to submit a new drug application (NDA) or supplement an existing NDA.

In the notice of proposed rulemaking (NPRM) for OTC vaginal contraceptive drug products (60 FR 6892, February 3, 1995), the agency proposed that manufacturers of OTC vaginal contraceptive drug products obtain approved NDAs for marketing of their products. The agency proposed this action because effectiveness of these products is dependent upon the final formulation. Therefore, the agency proposed that each product be tested in appropriate clinical trials under actual conditions of use.

In response to the NPRM, the agency is aware of ongoing clinical trials of vaginal contraceptives containing nonoxynol 9 (Refs. 1, 2, and 3). Pending the completion and analysis of these clinical trials, the agency is allowing the continued marketing of these products under the ongoing OTC drug review. These issues were discussed at the November 22, 1996, Nonprescription Drugs Advisory Committee (NDAC) meeting. NDAC concurred with the agency to allow interim marketing of nonoxynol 9 containing vaginal spermicides pending results from the proposed trials (Ref. 1). However, based on the studies discussed in section I of this document, the agency believes that vaginal contraceptive drug products containing nonoxynol 9 need to be labeled to inform users of these products that nonoxynol 9 does not prevent the transmission of the AIDS virus (HIV) and other STDs. Furthermore, users should be informed that frequent use of nonoxynol 9 can cause vaginal irritation and possibly increase the risk of becoming infected with the AIDS

virus (HIV) and other STDs from infected partners. This rulemaking addresses certain safety concerns with the use of nonoxynol 9.

Nonoxynol 9 is a nonionic surfactant that works as a vaginal contraceptive by damaging the cell membrane of sperm. It has been shown in certain in vitro studies to damage the cell wall of certain STD pathogens and to have activity against certain bacterial and viral STD pathogens, including HIV. However, based on the in vivo data described in section I of this document, the agency believes that this same cell membrane damaging effect can damage the vaginal and cervical epithelium (cell lining). Thus, nonoxynol 9 can have a negative impact on the vaginal lining and may increase the user's risk of getting STD/HIV and other genital infections. Irritation includes the range of physical findings from mild inflammation to epithelial disruption (damage to cells lining the vagina or cervix). Vaginal irritation may be symptomatic (with symptoms such as itching and burning) to asymptomatic (no symptoms).

Because nonoxynol 9 kills the AIDS virus (HIV) and other STD pathogens in vitro, it has been suggested, over the years, that the drug might help prevent or reduce the risk of transmission of the AIDS virus and other STDs in humans. Information currently available to the general public creates the misperception that nonoxynol 9 might help decrease the risk of becoming infected with the AIDS virus and other STDs (Refs. 4 through 7). Thus, the agency believes that this proposed rule is necessary to provide a clear, consistent message that nonoxynol 9 is not only ineffective in preventing HIV transmission, but that it could facilitate transmission of the disease.

At the International AIDS Conference (July 9–14, 2000), researchers from the Joint United Nations Programme on AIDS (UNAIDS) presented the preliminary findings of a 4-year study conducted in a very high-risk population

of 991 HIV negative female sex workers in Africa and Thailand to determine the effectiveness of a nonoxynol 9 gel (versus placebo) in preventing the transmission of HIV and STDs (Ref. 8). The test product contained 52.5 milligrams (mg) of nonoxynol 9 and a polymer with bioadhesive properties. The placebo contained only the polymer. Participants could be enrolled in the study if they did not use intravenous drugs or intravaginal spermicides other than the study drug. The participants reported an average of 3.6 partners per day and about 70 coital acts per month during the study. Condom use was encouraged. The preliminary study findings showed that women who used nonoxynol 9 gel had a higher incidence of new HIV infections (59) than those who used the placebo gel (41). Further, the more frequently women used only the nonoxynol 9 gel (without a condom to protect themselves), the higher their risk of becoming infected. Researchers also found that women who used nonoxynol 9 had more vaginal lesions, which might have facilitated the HIV transmission. Based on these preliminary study findings, on August 4, 2000, the Centers for Disease Control and Prevention (CDC) issued a letter (Ref. 9) stating "given that N-9 [nonoxynol 9] has now been proven ineffective against HIV transmission, the possibility of risk, with no benefit, indicates that N-9 should not be recommended as an effective means of HIV prevention." The final results of this study were recently published (Ref. 10) and substantiate the preliminary findings. The investigators stated that their data support the following conclusions: (1) Nonoxynol 9 increased the risk of HIV infection compared to placebo; (2) nonoxynol 9 had an adverse effect on vaginal epithelium when used frequently, thus increasing women's susceptibility to HIV; and (3) at low frequency use, nonoxynol 9 had no effect, either positive or negative, on HIV infection.

Earlier studies (Refs. 11 through 14) suggested that nonoxynol 9 vaginal spermicides may reduce gonococcal and chlamydial cervical infection and may even reduce the incidence of HIV infection. However, most of these studies did not assess the risk of acquiring HIV and the investigators stressed the need for more definitive randomized clinical trials. More recently, the International AIDS Conference report and the CDC letter (Refs. 8 and 9) have raised concerns that frequent use of nonoxynol 9 can increase vaginal and genital irritation and increase the risk of HIV transmission. Based on these safety concerns, the agency has reviewed studies on nonoxynol 9 conducted in Africa, Thailand, South America, Belgium, the Netherlands, and the United States that address the toxicity of the vaginal use of nonoxynol 9 in relation to dose, frequency of use, and the risk of becoming infected with STD/HIV.

Amaral et al. (Ref. 15) studied nonoxynol 9 in 18 women who were randomly and blindly assigned to an acid-buffering bioadhesive gel containing either 0 percent, 2.5 percent (125 mg), or 5 percent (250 mg) nonoxynol 9. Exclusion factors included a history of STD in the last 12 months, using any vaginal product within 7 days before admission to the study, or a known allergy to nonoxynol 9. Subjects were asked to abstain from sexual intercourse 48 hours before admission and during the study and not to use any other intravaginal products during the study. One dose of the assigned gel was administered vaginally daily for 6 days. No irritation or symptoms were reported by users of the acid-buffering bioadhesive gel without nonoxynol 9. Erythema in the vulva, cervix, and vagina was noted in all subjects using the acid-buffering vehicle containing nonoxynol 9 (2.5 percent and 5 percent). No signs of de-epithelialization or ulcers were seen in any of the subjects.

However, the authors concluded that the acid-buffering vehicle did not protect the cervix, vagina, and vulva from the irritation caused by nonoxynol 9.

Stafford et al. (Ref. 16) studied the effects of daily use for 7 days of a nonoxynol 9 (100 mg) containing gel versus placebo gel in 40 women who were not currently using any intravaginal products, did not have a current STD, had no history of genital ulcerative disease, and were not known to be HIV seropositive. The subjects were asked to avoid sexual intercourse during the treatment period. The nonoxynol 9 group had increased symptoms of irritation. Colposcopic (use of a magnifying instrument) and histologic (microscopic) examination of vaginal and cervical tissue showed evidence of inflammation in the genital tract. Also, a temporary reduction in the number of lactobacilli (bacteria found in the normal vaginal flora that appear to offer protective effects against the overgrowth of certain organisms that cause infection) was seen more frequently in the women using the nonoxynol 9 gel.

Rosenstein et al. (Ref. 17) studied the effect on normal vaginal flora of three intravaginal microbicides (dextrin sulfate, nonoxynol 9, or docusate sodium, in a gel dosage form) in three separate placebo-controlled studies. In these studies, women using dextrin sulfate gel were asked to insert 5 milliliters of the gel intravaginally for 4 consecutive nights and women using nonoxynol 9 gel and docusate sodium gel were asked to insert the respective gels for 7 consecutive nights. A reduction of lactobacilli occurred in 56 percent of women who used nonoxynol 9 and 63 percent of women who used docusate sodium. Women using nonoxynol 9 were also significantly more likely to become colonized abnormally than those using placebo. It appeared that women were more likely to have their vaginal flora return to normal after nonoxynol 9 treatment if the lactobacilli had not been depleted. The authors

expressed concern that continuous use of nonoxynol 9 would cause the vaginal flora to be altered persistently and, together with an increased risk of vaginal mucosal inflammation, could induce susceptibility to urinary and gynecological infection. The authors noted that it was essential that potential microbicides be examined for activity against normal vaginal flora.

In a single-blind crossover study of 33 women, Poindexter et al. (Ref. 18) compared three OTC vaginal spermicide formulations containing nonoxynol 9: A polycarbophil-based gel with 50 mg of nonoxynol 9, a cellulose-based gel with 100 mg of nonoxynol 9, and a polyurethane sponge with 1,000 mg of nonoxynol 9. The subjects refrained from coitus for 3 days prior to and during the 7 consecutive days of the treatment period. There was a 21-day washout period between each treatment. New gynecological abnormalities occurred in all three groups using nonoxynol 9. Abnormalities observed included redness, white epithelium, ulceration, mosaic petechiae, and squamous metaplasia. Redness was the most common abnormality. Ulceration was noted in 2 of the 31 users of the nonoxynol 9 cellulose-based gel formulation. The authors noted that the abnormal effects of the vaginal spermicides were more profound on the cervical mucosa than the vulvo-vaginal mucosa.

Coggins et al. (Ref. 19) studied the safety of three vaginal spermicides containing nonoxynol 9: Film (70 mg), suppositories (150 mg), and gel (200 mg). Each woman used each product for a 4-week period and reported to the study center every 2 weeks. The authors did not indicate if there was a washout period between treatments. To avoid the potential for irritation from frequent use of nonoxynol 9 containing products, only women whose average coital frequency was one or fewer acts of intercourse per day were eligible



to be enrolled. In this study, no ulcers or genital lesions were detected and clinical signs of irritation were fairly uncommon and not frequent when compared to baseline. The authors concluded that these products are safe for low frequency use.

Watts et al. (Ref. 20) evaluated the effects of nonoxynol 9 on the vaginal flora and epithelium of 48 women (16 in each group) after application of a single dose and in the absence of sexual intercourse. Quantitative vaginal cultures and colposcopy were done at baseline and at 0.5, 4, 24, 48, and 72 hours after insertion of one of three commercially available vaginal spermicides containing nonoxynol 9 (200-mg gel, 52.5-mg gel, or 70-mg film). Symptoms and colposcopic abnormalities were rare after use of nonoxynol 9. The proportion of women with *Escherichia coli* (*E. coli*) increased with the gel containing 200 mg of nonoxynol 9 per dose and the concentration of *E. coli* increased with all of the test products. The authors noted that the transient decreased concentration of lactobacilli and increased levels of *E. coli* seen with all three test products are of concern and likely are intensified and perpetuated with repeated use of nonoxynol 9 as a microbicide. The authors suggested that adverse effects may be enhanced with frequent or chronic use and that chronic use may cause changes in the vaginal flora that may lead to urinary tract infection and other resultant complications.

Niruthisard et al. (Ref. 21) conducted a double-blind, local toxicity study on the effects of frequent use of nonoxynol 9 in 20 women who were not considered to be at high risk for STDs. Fifteen women used 150-mg nonoxynol 9 containing suppositories and 5 women used placebos (lubricating suppositories) inserted vaginally hourly for 4 consecutive hours each day for 14 consecutive days. The study concluded that none of the women who used

the placebo suppositories had abnormal physical findings. Six women who used the nonoxynol 9 suppositories had physical findings, including epithelial disruption and/or bleeding. In four women, the break in the cervical epithelium appeared to be the result of the sloughing of a thin layer of cells. One woman had bleeding and sloughing of her vaginal mucosa and another had a severe reaction on her cervix that was bleeding and edematous. All of these adverse events resolved within 1 week of stopping nonoxynol 9 use. The authors cautioned that this pilot study should be confirmed by other trials and that these findings may not be extrapolated to other situations of nonoxynol 9 use.

Roddy et al. (Ref. 22) followed up with a study in 175 women to evaluate effects of dosing on vaginal and cervical irritation using a vaginal suppository with 150 mg of nonoxynol 9 at various dosing frequencies for 2 weeks. The women agreed to refrain from sexual intercourse and douching during the study period. Clinical signs of genital irritation included erythema and epithelial disruption. Erythema in the vagina was the major clinical sign noted. Epithelial disruption was defined as a break in the epithelium lining of the vulva, vagina, or cervix. Women with vulvar irritation also had vaginal and cervical irritation. The symptoms that were attributed to genital irritation included dysuria, genital itching, and burning. The irritation from using nonoxynol 9 every other day was no different than using the placebo. Use of nonoxynol 9 once or twice a day increased the rate of epithelial disruption. Use of nonoxynol 9 four times a day increased the rate of epithelial disruption about five times that of the placebo. However, the authors noted that having symptoms was not predictive of clinical signs and women with obvious clinical signs did not always report symptoms. The authors stated that there

is no conclusive evidence of a dose response, but the data suggest a stepwise increase in signs of irritation with an increasing number of doses per day.

Van Damme et al. (Ref. 23) conducted a multicenter, randomized, double-blind, controlled trial with three groups (52.5-mg nonoxynol 9 gel, placebo gel, and a no-treatment control), examining the use of a lower dose of nonoxynol 9 in 534 women at low risk of HIV infection. The subjects were healthy women with no evidence of STDs and no clinical or colposcopic abnormalities. The subjects were to apply the study products once daily at the same time each day for 14 days and were allowed to have sexual intercourse. Incidences of genital symptoms such as vaginal discharge, erythema, lesions, and petechial hemorrhage (the most frequent abnormality reported) were significantly greater in the group using the nonoxynol 9 gel than the other groups. Women in the group using the nonoxynol 9 gel were significantly more likely to develop a lesion than those in either the placebo or no-treatment group. The authors noted that the clinical significance is unclear with regard to the excess incidence of petechial hemorrhage in the nonoxynol 9 group and of other types of lesions that were not associated with epithelial disruption. The authors stated that, in theory, it is possible that any type of genital lesion may increase a woman's risk of becoming infected with HIV, especially if it serves as a focus for the recruitment of HIV-infectable inflammatory cells. However, they stated that whether this is of significance will need to be ascertained by large-scale intervention trials in populations at high risk of HIV infection.

The incidence of ulceration, abrasion, and STD or other genital infections was low for all three treatment groups. The authors suggested that these findings were the result of the once a day application of the nonoxynol 9 and that at this frequency of use the nonoxynol 9 gel can be considered safe. The

authors also stated that having established the safety of a single application, it was important to evaluate the effects of multiple doses. They noted that a study, which was not cited, involving the application of the same nonoxynol 9 gel four times daily had recently been completed.

Kreiss et al. (Ref. 24) studied 138 HIV seronegative female sex workers at very high risk of HIV seroconversion who were randomly assigned to a nonoxynol 9 (1,000 mg) containing vaginal sponge or placebo (glycerin vaginal suppository containing mineral oil, subsequently a water-based vaginal cream was used). Subjects were instructed to insert a sponge before the first sex partner each day, replace the sponge after every two to three partners, and remove the sponge 6 hours after the last sex partner. All subjects were intensively counseled and urged to have each sexual partner use condoms. Women in the study used the sponge an average of 14 times per week. Women were asked to return for followup at monthly intervals or more frequently if needed. The duration range for followups was between 1 and 46 months. The mean (average) duration period of followup was 14 months for the nonoxynol 9 group and 17 months for the placebo group. Spermicide-attributed complaints, mostly vulvar irritation, burning, and ulceration, were reported in 47 percent of the nonoxynol 9 users and 7 percent of the placebo users. There was a higher seroconversion (i.e., testing showing conversion from HIV negative to HIV positive) in women using the nonoxynol 9 containing sponge than the placebo product. Because of concern regarding the adverse local effects of the nonoxynol 9 (1,000 mg) containing sponge, and its potential for increasing the risk of HIV transmission, rather than being protective, the study was prematurely terminated.

Martin et al. (Ref. 25) studied the use of a nonoxynol 9 gel (52.5 mg) in 52 HIV seronegative female sex workers. Subjects had to be free of STDs and any evidence of genital epithelial disruption, and had to report 100 percent compliance with condom use. Subjects were randomized to the nonoxynol 9 gel or to a placebo group and used one applicatorful per day. After a 14-day washout period, the subjects used the other treatment for 14 days. Subjects were evaluated by a questionnaire and physical examinations, including colposcopy. The authors concluded that daily application of the 52.5-mg nonoxynol 9 gel was safe, but they made no extrapolations to more frequent use. However, the authors acknowledged the shortness of the duration of use and that the power of this study to detect a small increase in epithelial toxicity might be limited.

Roddy et al. (Ref. 26) studied the use of a nonoxynol 9 containing film as a vaginal microbicide in 1,295 HIV-negative female sex workers. In a double-blind, placebo-controlled study, the subjects were instructed to have their male sexual partners use latex condoms and were randomly assigned to use either the nonoxynol 9 film or a placebo film. At monthly followup visits, the women were examined with a colposcope for genital lesions and were tested for gonorrhea, chlamydia, and HIV infection. Seventy-three percent of the women remained in the study for 12 months with a mean followup period of approximately 14 months. The authors concluded that the use of the nonoxynol 9 vaginal film did not reduce the rate of new HIV, gonorrhea, or chlamydia infection even in those that used latex condoms and who received treatment for STDs.

Van Damme et al. (Ref. 27) looked at more frequent use of the nonoxynol 9 (52.5 mg) gel among 320 HIV-seronegative female sex workers who did not

have clinical STDs, genital ulcers, or abrasions, did not use illicit drugs, and participated in a 100 percent condom-use program. The study was designed as a randomized, placebo-controlled, triple-blind trial to assess the effect of nonoxynol 9 gel in the prevention of HIV/STD infection. Subjects were instructed to apply the test product or the placebo (gel vehicle without the nonoxynol 9) and to have their male sexual partners use a condom for every sex act. There were major differences in condom use between the study centers. The mean number of applicators of the daily gel use was 1.2 and 1.3, respectively, in the treatment and placebo groups. Colposcopy examinations showed that vaginal irritation, such as ulcerations, abrasions (on the cervix and external genitalia), lesions, and erythema, was observed in both the treatment and the placebo groups. However, based on the number and incidences of colposcopic lesions per followup period of up to 12 weeks, the incidence of colposcopic lesions was low and there was no difference between the treatment groups. The authors reported that in both groups the chance of having a lesion increased with an increase in the mean daily use of the product. The authors concluded that multiple daily use of the nonoxynol 9 containing gel did not show an increase of local toxicity over the placebo gel.

Rustomjee et al. (Ref. 28) studied a vaginal contraceptive film containing 72 mg of nonoxynol 9 versus a glycerin placebo film in a randomized, double-blind, crossover trial. The 20 subjects were female sex workers, and HIV infection was not an exclusion criteria. Subjects used either the treatment film or placebo film for 1 month and, after a 1-month film-free washout period, used the other film for the last month. Condoms were provided. The differences in signs and symptoms of genital lesions from use of the nonoxynol 9 film and the placebo film did not reach statistical significance. However,

the authors cautioned that the clinical findings of an increase in minor erythematous genital lesions in the nonoxynol 9 group, together with an increased HIV viral load associated with the presence of a minor genital lesion, is worrisome.

In summary, many of the studies (Refs. 8, 15 through 18, 20 through 24, and 28) suggest that nonoxynol 9 vaginal contraceptive formulations can increase the chances of vaginal and genital tract irritation, and cause disruption of the vaginal epithelium or the vaginal flora. Some studies (Refs. 8, 20, 22, and 23) suggest the risk of these adverse events can be increased by frequent and/or chronic use. One study (Ref. 25) concluded that once a day use was safe, but noted that the power to detect a small increase in epithelial toxicity may be limited by the short duration of use. Investigators in one study (Ref. 27) concluded that multiple daily use of nonoxynol 9 (52.5 mg) gel was safe, but in a previous study (Ref. 23) of nonoxynol 9 (52.5 mg) gel in women with low risk of HIV infection, the investigators concluded that women using nonoxynol 9 gel were significantly more likely to develop lesions than those in the placebo or no-treatment groups. The authors stated that large scale intervention trials were needed to determine if genital lesions increase the risk of acquiring HIV infection.

Several studies suggested a causal link between the frequency of use of nonoxynol 9, increased vaginal irritation, and the possibility that vaginal irritation (such as the disruption of the vaginal epithelium) may increase the risk of transmission of the AIDS virus (HIV) and other STDs. The preliminary findings of a study on nonoxynol 9 (52.5 mg) gel presented at the International AIDS Conference in July 2000 (Ref. 8) suggested that nonoxynol 9 does not prevent the transmission of HIV and other STDs and may facilitate the

transmission of these pathogens. Another study (Ref. 26) concluded that the use of a nonoxynol 9 containing film did not reduce the rate of new HIV, gonorrhea, or chlamydia infection even when latex condoms were used. Other studies (Refs. 20, 24, and 28) also suggested that the adverse effects of nonoxynol 9 on the vaginal flora and epithelium may increase the risk of transmission of the AIDS virus (HIV), certain other STDs, and/or genital infections. The studies in high risk populations (sex workers) (Refs. 8, 24, 25, 27, and 28) suggested the possibility that the frequency of use of nonoxynol 9 can increase vaginal irritation and epithelium disruption. Such increased irritation may increase the risk of becoming infected with STDs, including the AIDS virus (HIV) from infected partners.

The CDC, on May 10, 2002, published a report containing a recommendation that women, particularly those at risk for HIV or STDs, be informed that nonoxynol 9 contraceptives do not protect against these infections (Ref. 29). The CDC report described the extent of nonoxynol 9 contraceptive use in women in 1999 and summarized recent publications on nonoxynol 9 and HIV/STDs. According to this report, most women in the United States with HIV become infected through sexual transmission. Thus, the report underscores the importance of alerting women about the safety concerns surrounding nonoxynol 9.

On June 28, 2002, the World Health Organization (WHO) issued revised public health guidelines for the use of nonoxynol 9 for HIV and STD prevention and for pregnancy prevention in populations at high risk for HIV (Ref. 30). The guidelines were based on a review of current clinical safety and effectiveness data on nonoxynol 9 (Ref. 31). The WHO guidelines advised that “Spermicides containing nonoxynol 9 do not protect against HIV infection and



may even increase the risk of HIV infection in women using these products frequently.” The guidelines also advised women at high risk of HIV infection against using nonoxynol 9 spermicides for contraception.

Based on safety concerns, the agency considers it important to alert users of OTC vaginal contraceptives containing nonoxynol 9 that these products do not prevent transmission of the AIDS virus (HIV) and other STDs, and that frequent use of these products can increase vaginal irritation, which may increase the risk of getting certain STDs, including the AIDS virus (HIV) from infected partners. The agency also believes that product labeling should include a statement to encourage the use of condoms as a method to help reduce the risk of becoming infected with the AIDS virus (HIV) and other STDs.

FDA’s proposal to require these warnings and other information does not require a finding that any or all of the OTC drug products that contain nonoxynol 9 actually caused an adverse event, and FDA does not so find. Nor does FDA’s requirement of warnings and other information repudiate the OTC drug monographs under which the affected drug products have been lawfully marketed. Rather, as a consumer protection agency, FDA has determined that these additional warnings and other information are necessary to ensure that these OTC drug products continue to be safe and effective for their labeled indications under ordinary conditions of use as those terms are defined in the Federal Food, Drug, and Cosmetic Act. This judgment balances the benefits of these drug products against their potential risks, and reflects our conclusion that even a potential link between the use of nonoxynol 9 and serious adverse health consequences warrants this action (see CFR 330.10(a)).

FDA's decision to act in an instance such as this one need not meet the standard of proof required to prevail in a private tort action (*Glastetter v. Novartis Pharmaceuticals, Corp.*, 252 F.3d 986, 991 (8th Cir. 2001)). To mandate a warning, or take similar regulatory action, FDA need not show, nor do we allege, actual causation.

In the NPRM (60 FR 6892 at 6901), the agency stated that consumers should be warned about possible allergic reactions such as burning and itching of the vagina and penis that may occur when using vaginal contraceptive drug products. The agency recommended that the following warning be included in the labeling: "If you or your partner develops irritation, such as burning or itching in the genital area, stop using this product. If irritation continues, contact your physician." At the November 22, 1996, NDAC meeting (Ref. 1), the committee also noted that penile irritation could occur. The agency is aware that the labeling of most OTC marketed vaginal spermicides containing nonoxynol 9 bears a warning to stop use and ask a doctor if irritation of the vagina or penis occurs or continues. In this document, the agency is proposing a similar warning. The agency is not aware of any data that suggest increased penile irritation from frequent use of nonoxynol 9 may increase the risk of getting STDs from infected female partners. However, the agency encourages more research and studies to evaluate this potential safety concern.

## **II. The Agency's Proposal**

The agency is proposing to amend part 201 (21 CFR part 201) by adding § 201.325 entitled "Over-the-counter drugs for vaginal contraceptive use containing nonoxynol 9 as the active ingredient; required warnings." This section would require new warnings for all OTC vaginal contraceptive drug products containing nonoxynol 9 as the active ingredient, whether marketed

under an NDA or the ongoing OTC drug review. The agency is proposing to require the following warnings be added to the labeling of all marketed OTC vaginal contraceptives containing nonoxynol 9: “Sexually transmitted diseases (STDs) alert [heading in bold type]: This product does not [this word highlighted in bold type] protect against the AIDS virus (HIV) or other sexually transmitted diseases (STDs).”

Based on the studies, the agency is also proposing a warning to inform users of OTC vaginal spermicides containing nonoxynol 9 that frequent use can increase vaginal irritation and may increase the risk of getting the AIDS virus (HIV) or other STDs from infected partners. The statements would also quantify the definition of “frequent use” by adding “(more than once a day)”. The proposed warning states:

Ask a doctor before use if you have [heading in bold type] a new sex partner, multiple sex partners, or unprotected sex. Frequent use (more than once a day) of this product can increase vaginal irritation, which may increase the risk of becoming infected with the AIDS virus (HIV) or other STDs from infected partners. Ask a doctor or other health professional for your best birth control method.

The agency is also proposing a warning to stop use and ask a doctor if irritation of the vagina or penis occurs. The agency recommended a similar warning in the NPRM (60 FR 6892 at 6901): “If you or your partner develops irritation, such as burning or itching in the genital area, stop using this product. If irritation continues, contact your physician.” The agency is revising that warning in this document to state: “Stop use and ask a doctor if [heading in bold type] you or your partner get burning, itching, a rash, or other irritation of the vagina or penis.” Further, the warning that reads “For vaginal use only” needs to be included in accordance with the requirements in § 201.66(c)(5)(i).

Because of the public health concerns regarding the transmission of STDs and the AIDS virus (HIV), the agency believes that manufacturers should inform consumers as soon as possible that nonoxynol 9 does not protect against the AIDS virus (HIV) and that frequent use of nonoxynol 9 can increase vaginal irritation. FDA encourages manufacturers of all OTC vaginal contraceptive drug products containing nonoxynol 9 to implement the agency's proposed labeling warnings voluntarily as soon as possible, subject to the possibility that FDA may change the wording of the statements, as a result of comments submitted in response to this proposal. The agency considers these warnings important to the safe use of OTC vaginal contraceptive drug products containing nonoxynol 9.

Because there is no final monograph for these products at present, manufacturers of OTC vaginal contraceptive drug products containing nonoxynol 9 are required to follow the labeling requirements in § 201.66 as of the first major labeling revision after May 16, 2002. The agency intends to consider the labeling revisions in this proposal, when finalized, to be the first major labeling revision after May 16, 2002, for products that have not already converted to the "Drug Facts" labeling format, and to require those products to conform to § 201.66 at that time. For products that have already converted to the "Drug Facts" format, the agency will require the labeling revisions in this proposal to be implemented by the effective date of the final rule.

In addition, the agency is proposing to require additional labeling information which would convey to consumers that studies have raised safety concerns that increased vaginal irritation (i.e., irritation or damage to the cell lining of the vagina that may or may not produce symptoms) caused by frequent use of nonoxynol 9 may make one more susceptible to the risk of

getting the AIDS virus (HIV) or other STDs from infected partners and that consumers who use these products frequently should seek further advice from a doctor or other health professional for their best birth control method. In the interest of public health, the information would also include a statement to encourage the use of a latex condom with every sexual act to help to reduce the risk of getting the AIDS virus (HIV) and other STDs. The agency is proposing that this labeling be included either on the outside container or wrapper of the retail package under the "Other information" section of the "Drug Facts" labeling in accordance with § 201.66 or in a package insert. Many of the marketed OTC vaginal contraceptive drug products already have a package insert that contains information on how to use the product and this new information could readily be incorporated in that package insert. The agency is proposing the following labeling:

- Studies have raised safety concerns that frequent use (more than once a day) of products containing nonoxynol 9 can increase vaginal irritation, which may increase the risk of getting the AIDS virus (HIV) or other STDs from infected partners. Vaginal irritation may include symptoms such as burning, itching, or a rash, or you may not notice any symptoms at all. If you use these products frequently and/or have a new sex partner, multiple sex partners, or unprotected sex, see a doctor or other health professional for your best birth control and methods to prevent STDs.

- Correct use of a latex condom with every sexual act will help reduce the risk of getting the AIDS virus (HIV) and other STDs.

The studies suggest a possible correlation between increased vaginal irritation from frequent use and the risk of transmission of the AIDS virus (HIV) and other STDs. Because of this significant safety concern, the agency is asking for comments on how to best present this information in the product labeling.

### III. Questions to be Addressed

The agency is concerned with how well consumers understand the language in the proposed warnings and whether the proposed warnings convey the safety concerns for nonoxynol 9 adequately. The agency invites public comments on the following questions:

1. Do the proposed warnings under the headings “Sexually transmitted diseases alert,” “Ask a doctor before use if you have,” and “Stop use and ask a doctor if” adequately convey the safety concerns to consumers? What revisions, if any, would be useful?

2. Are there other data to support, expand, or refute the proposed warnings?

3. Are there additional data to further clarify or specifically quantify the term “frequent use” in the proposed warning that states: “Frequent use (more than once a day) of this product can increase vaginal irritation, which may increase the risk of getting the AIDS virus (HIV) or other STDs from infected partners”?

4. Are the symptoms of vaginal irritation adequately defined? Are there other symptoms that should be included?

5. Are there additional data to correlate an increase in vaginal irritation with an increased risk of transmission of HIV and other STDs? If so, how should such information be conveyed in labeling?

6. Is a package insert the best way to provide additional information to consumers or should this information appear on the outer carton?

7. Are the proposed statements for the package insert appropriate? What revisions or additional information, if any, would be useful to make the package insert more informative and consumer friendly?

#### IV. Analysis of Impacts

FDA has examined the impacts of this proposed rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (2 U.S.C. 1501 *et seq.*). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Under the Regulatory Flexibility Act, if a rule has a significant impact on a substantial number of small entities, an agency must analyze regulatory options that would minimize any significant impact of the rule on small entities. Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement of anticipated costs and benefits before proposing any rule that may result in an expenditure in any one year by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100 million (adjusted annually for inflation).

The agency believes that this proposed rule is consistent with the principles set out in Executive Order 12866 and in these two statutes. FDA has determined that the proposed rule is not a significant regulatory action as defined by the Executive order and so is not subject to review under the Executive order.

The Unfunded Mandates Reform Act does not require FDA to prepare a statement of costs and benefits for this proposed rule, because the proposed rule is not expected to result in any 1-year expenditure that would exceed \$100 million adjusted for inflation. The current inflation adjusted statutory threshold is about \$110 million.

The purpose of this proposed rule is to require additional labeling for OTC vaginal contraceptive drug products containing nonoxynol 9. The labeling includes new warnings and other important information about using these products. These products are currently packaged in an outer carton that should have sufficient space to accommodate this additional labeling. The agency is aware that most of the currently marketed products already include a consumer package insert. Therefore, to allow firms greater flexibility, the agency is allowing almost half of the new information to appear in the package insert. There are a limited number of products currently marketed that will be affected by this proposed rule and the incremental one-time costs are minimal. The one-time costs include designing the new carton, designing a new package insert, and the inventory loss of any unused current labeling. The agency assumes the same weighted average cost to relabel (i.e., \$3,600 per stock keeping unit (SKU) (individual products, packages, and sizes)) that it estimated for the final rule requiring uniform label formats of OTC drug products (64 FR 13254 at 13279 to 13281, March 17, 1999). Inventory loss was estimated using data from a study supporting the fore mentioned rule. With a 6-month implementation period, inventory loss was estimated to be between \$500 and \$3,000 per SKU, depending on product sales, for an estimated weighted average inventory loss of \$2,050 . The inventory loss and redesign costs for the package insert are estimated to be about \$1,380 per SKU.

The agency's Drug Listing System identifies 15 manufacturers and distributors of OTC vaginal contraceptive drug products containing nonoxynol 9 that together produce approximately 40 SKUs. At a relabeling cost of \$3,600 per SKU and an inventory loss of \$2,050 per SKU, estimated total one-time costs of relabeling could be \$266,000 ( $40 \times (\$3,600 + \$2,050)$ ). Even if all



required wording is revised on the outer carton, manufacturers may revise their package inserts as well to conform to the revised language. This adds another \$55,200 ( $40 \times \$1,380$ ) to the one-time cost, for an estimated total of \$321,200.

As the agency is providing the language of the labeling to be used, all firms should have the necessary skills and personnel to perform the required relabeling either in-house or by contractual arrangement. The proposed rule does not require any new reporting or recordkeeping activities. No additional professional skills are needed.

About 9 firms affected by this proposed rule meet the Small Business Administration's definition of a small entity (fewer than 750 employees). The actual impact on these firms will vary depending on the number and nature of the products they manufacture or distribute. All nine entities market additional types of products and have only one or two SKUs affected by this proposed rule. The average incremental cost per SKU to comply with this proposed rule is estimated to be \$8,030 ( $\$321,200/40$  SKUs). Actual costs to the small entities will likely be lower because distributors of low sales volume OTC drug products usually market their products in packaging that costs less than the industry average.

While the costs to individual manufacturers to relabel their products are minimal, the potential benefits to consumers who use these products are substantial. The agency considers it essential that users be aware that these products do not protect against the AIDS virus (HIV) or other STDs. The monetary benefit of potentially preventing any cases of AIDS or STDs is significant compared to the minor cost of relabeling these products to provide the new required information.

The agency has tentatively considered but rejected several labeling alternatives: (1) A shorter or longer implementation period, and (2) an exemption from coverage for small entities. The agency considers it important that this information appear in product labeling as soon as possible, but acknowledges that implementation in a timeframe any less than 6 months would be very difficult for affected manufacturers. However, because of the importance of this new labeling information, the agency considers a period of 12 months too long to implement this new labeling. The agency rejected an exemption for small entities because the new labeling is also needed by consumers who purchase products marketed by those entities. Further, because of the importance of this information, the agency is not proposing a longer effective date for any products with annual sales less than \$25,000.

The analysis shows that this proposed rule is not economically significant under Executive Order 12866 and that the agency has considered the burden to small entities. Based on this analysis, the agency does not believe manufacturers will incur a significant economic impact. Therefore, the agency certifies that the proposed rule will not have a significant economic impact on a substantial number of small entities. No further analysis is required under the Regulatory Flexibility Act (5 U.S.C. 605(b)).

The agency invites public comment regarding any substantial or significant economic impact that this proposed rule would have on companies marketing OTC vaginal contraceptive drug products containing nonoxynol 9. Types of impact may include, but are not limited to, costs associated with relabeling or repackaging. Comments regarding the impact of this proposed rule should be accompanied by appropriate documentation. The agency is providing a period of 90 days from the date of publication of this proposed rule in the

**Federal Register** for comments on this subject to be developed and submitted.

The agency will evaluate any comments and supporting data that are received and will reassess the economic impact of this proposed rule in the preamble to the final rule.

## **V. Paperwork Reduction Act of 1995**

FDA tentatively concludes that the labeling requirements proposed in this document are not subject to review by the Office of Management and Budget because they do not constitute a “collection of information” under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501 *et seq.*). Rather, the proposed labeling statements are a “public disclosure of information originally supplied by the Federal government to the recipient for the purpose of disclosure to the public” (5 CFR 1320.3(c)(2)).

## **VI. Environmental Impact**

The agency has determined under 21 CFR 25.31(a) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

## **VII. Federalism**

FDA has analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the proposed rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the agency tentatively concludes that the proposed

rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement has not been prepared.

### **VIII. Request for Comments**

Interested persons may submit written or electronic comments on the proposed rule, the agency's specific questions in section III of this document, and the agency's economic impact determination to the Dockets Management Branch (see **ADDRESSES**) by *[insert date 90 days after date of publication in the Federal Register]*. Three copies of all written comments are to be submitted. Individuals submitting written comments or anyone submitting electronic comments may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Received comments may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

### **IX. Proposed Effective Date**

Because of the importance of the proposed warnings to the safe use of OTC vaginal contraceptive drug products containing nonoxynol 9, the agency is proposing that any final rule that may publish based on this proposal become effective 6 months after its date of publication in the **Federal Register**.

### **X. References**

The following references are on display in the Dockets Management Branch (see **ADDRESSES**), under Docket No. 80N-0280, and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. FDA, Transcript of Joint Meeting of the Nonprescription Drugs, Reproductive Health Drugs, Anti-Infective Drugs and Antiviral Drugs Advisory Committees, in OTC vol. 11ATFM3, November 22, 1996.

2. Letter from D. L. Bowen, FDA, to R. W. Soller, Nonprescription Drug Manufacturers Association, coded LET 6.

3. Letter from D. L. Bowen, FDA, to R. W. Soller, Nonprescription Drug Manufacturers Association, coded LET 7.

4. Jim Shelton's Pearls for July 2000, "Spermicides and Protection Against STDs," Johns Hopkins Center for Communication Programs, in OTC vol. 11ATFM3, 2000.

5. Jim Shelton's Pearls for September 2000, "Nonoxynol-9 and HIV Transmission," Johns Hopkins Center for Communication Programs, in OTC vol. 11ATFM3, 2000.

6. University of Florida, "HIV/AIDS Information/Resources."

7. Drugs.com (Drug Information Online), "Spermicides Vaginal," in OTC vol. 11ATFM3.

8. Van Damme, L., "Advances in Topical Microbicides," presented at the XIII International AIDS Conference, Durban, South Africa, July 9–14, 2000.

9. Letter from H. D. Gayle, National Center for HIV, STD, and TB Prevention, Centers for Disease Control and Prevention, in OTC vol. 11ATFM3, August 4, 2000.

10. Van Damme, L. et al, "Effectiveness of COL-1492, a Nonoxynol-9 Vaginal Gel, on HIV-1 Transmission in Female Sex Workers: A Randomised Controlled Trial," *The Lancet*, 360:974–977, 2002.

11. Austin, H., W. C. Louv, and W. J. Alexander, "A Case-Control Study of Spermicides and Gonorrhea," *Journal of the American Medical Association*, 251:2822–2824, 1984.

12. Rosenberg, M. J. et al., "Effect of the Contraceptive Sponge on Chlamydial Infection, Gonorrhea, and Candidiasis," *Journal of the American Medical Association*, 257:2308–2313, 1987.

13. Niruthisard, S., R. E. Roddy, and S. Chutivongse, "Use of Nonoxynol-9 and Reduction in Rate of Gonococcal and Chlamydial Cervical Infections," *The Lancet*, 339:1371–1376, 1992.
14. Zekeng, L. et al., "Barrier Contraceptive Use and HIV Infection Among High Risk Women in Cameroon," *AIDS*, 7:725–731, 1993.
15. Amaral, E. et al., "Study of the Vaginal Tolerance to Acidform, an Acid Buffering Gel," *Contraception*, 60(6):361–366, 1999.
16. Stafford, M. K. et al., "Safety Study of Nonoxynol-9 as a Vaginal Microbicide; Evidence of Adverse Effects," *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology*, 17:327–331, 1998.
17. Rosenstein, I. J. et al., "Effect on Normal Vaginal Flora of Three Intravaginal Microbicidal Agents Potentially Active Against Human Immunodeficiency Virus Type 1," *The Journal of Infectious Diseases*, 177:1386–1390, 1998.
18. Poindexter III, A. N. et al., "Comparison of Spermicides on Vulvar, Vaginal, and Cervical Mucosa," *Contraception*, 53:147–153, 1996.
19. Coggins, C. et al., "Safety of Three Formulations of Nonoxynol-9 Containing Vaginal Spermicides," *International Journal of Gynecology and Obstetrics*, 68:267–268, 1999.
20. Watts, H. et al., "The Effects of Three Nonoxynol-9 Preparations on Vaginal Flora and Epithelium," *The Journal of Infectious Diseases*, 180:426–437, 1999.
21. Niruthisard, S., R. E. Roddy, and S. Chutivongse, "The Effects of Frequent Nonoxynol-9 Use on the Vaginal and Cervical Mucosa," *Journal of the American Venereal Disease Association*, 18:176–179, 1991.
22. Roddy, R. E. et al., "A Dosing Study of Nonoxynol-9 and Genital Irritation," *International Journal of STD and AIDS*, 4:165–170, 1993.
23. Van Damme, L. V. et al., "Safety Evaluation of Nonoxynol-9 Gel in Women at Low Risk of HIV Infection," *AIDS*, 12:433–437, 1998.

24. Kreiss, J. et al., "Efficacy of Nonoxynol 9 Contraceptive Sponge Use in Preventing Heterosexual Acquisition of HIV in Nairobi Prostitutes," *Journal of the American Medical Association*, 268:477–482, 1992.
25. Martin, H. L. et al., "Safety of a Nonoxynol-9 Vaginal Gel in Kenyan Prostitutes," *Sexually Transmitted Diseases*, 24(5):279–283, 1997.
26. Roddy, R. E. et al., "A Controlled Trial of Nonoxynol 9 Film to Reduce Male-to-Female Transmission of Sexually Transmitted Diseases," *New England Journal of Medicine*, 339(8):504–510, 1998.
27. Van Damme, L. V. et al., "Safety of Multiple Daily Applications of COL-1492, A Nonoxynol-9 Vaginal Gel, Among Female Sex Workers," *AIDS* 2000, 14(1):85–88, 2000.
28. Rustonjee, R. et al., "Phase 1 Trial of Nonoxynol 9 Film Among Sex Workers in South Africa," *AIDS*, 13:1511–1515, 1999.
29. CDC, "Nonoxynol-9 Spermicide Contraception Use—United States, 1999," *Morbidity and Mortality Weekly Report*, 51(18): 389–392, 2002.
30. WHO, "Nonoxynol-9 Ineffective in Preventing HIV Infection," May 28, 2002.
31. WHO, "WHO/CONRAD Technical Consultation on Nonoxynol-9, Summary Report," 2001.

## **List of Subjects in 21 CFR Part 201**

Drugs, Labeling, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 201 be amended as follows:

### **PART 201—LABELING**

1. The authority citation for 21 CFR part 201 continues to read as follows:

**Authority:** 21 U.S.C. 321, 331, 351, 352, 353, 355, 358, 360b, 360gg–360ss, 371, 374, 379e; 42 U.S.C. 216, 241, 262, 264.

2. Section 201.66 is amended by adding paragraph (c)(5)(ii)(H) to read as follows:

**§ 201.66 Format and content requirements for over-the-counter (OTC) drug product labeling.**

\* \* \* \*

(c) \* \* \*

(5) \* \* \*

(ii) \* \* \*

(H) Sexually transmitted diseases (STDs) warning for vaginal contraceptive drug products containing nonoxynol 9 set forth in § 201.325(b)(2). This warning shall follow the subheading “Sexually transmitted diseases (STDs) alert:”

3. Section 201.325 is added to subpart G to read as follows:

**§ 201.325 Over-the-counter drugs for vaginal contraceptive use containing nonoxynol 9 as the active ingredient; required warnings.**

(a) Studies indicate that use of vaginal contraceptives containing nonoxynol 9 does not protect against infection from the human immunodeficiency virus (HIV), the virus that causes acquired immunodeficiency syndrome (AIDS), or against the transmission of other sexually transmitted diseases (STDs). Studies also suggest that frequent use of vaginal contraceptives containing nonoxynol 9 can increase vaginal irritation, such as the disruption of the vaginal epithelium. These effects may increase the risk of transmission of the AIDS virus (HIV) and other STDs from an infected partner. Consumers should be warned that these products do not protect against the transmission of the AIDS virus (HIV) or other STDs. In



addition, frequent use of these products can increase vaginal irritation, which may increase the risk of getting certain STDs, including the AIDS virus (HIV), from infected partners.

(b) The labeling of OTC vaginal contraceptive drug products containing nonoxynol 9 as the active ingredient, whether subject to the ongoing OTC drug review or an approved drug application, must contain the following warnings under the heading “Warnings,” in accordance with § 201.66.

(1) “For vaginal use only” [this heading in bold type]

(2) “Sexually transmitted diseases (STDs) alert [this heading in bold type]:

This product does not [this word in bold type] protect against the AIDS virus (HIV) or other STDs.”

(3) “Ask a doctor before use if you have [heading in bold type] [optional, bullet] a new sex partner, multiple sex partners, or unprotected sex. Frequent use (more than once a day) of this product can increase vaginal irritation, which may increase the risk of getting the AIDS virus (HIV) or other STDs from infected partners. Ask a doctor or other health professional for your best birth control method.”

(4) “Stop use and ask a doctor if [heading in bold type] [optional, bullet] you or your partner get burning, itching, a rash, or other irritation of the vagina or penis”.

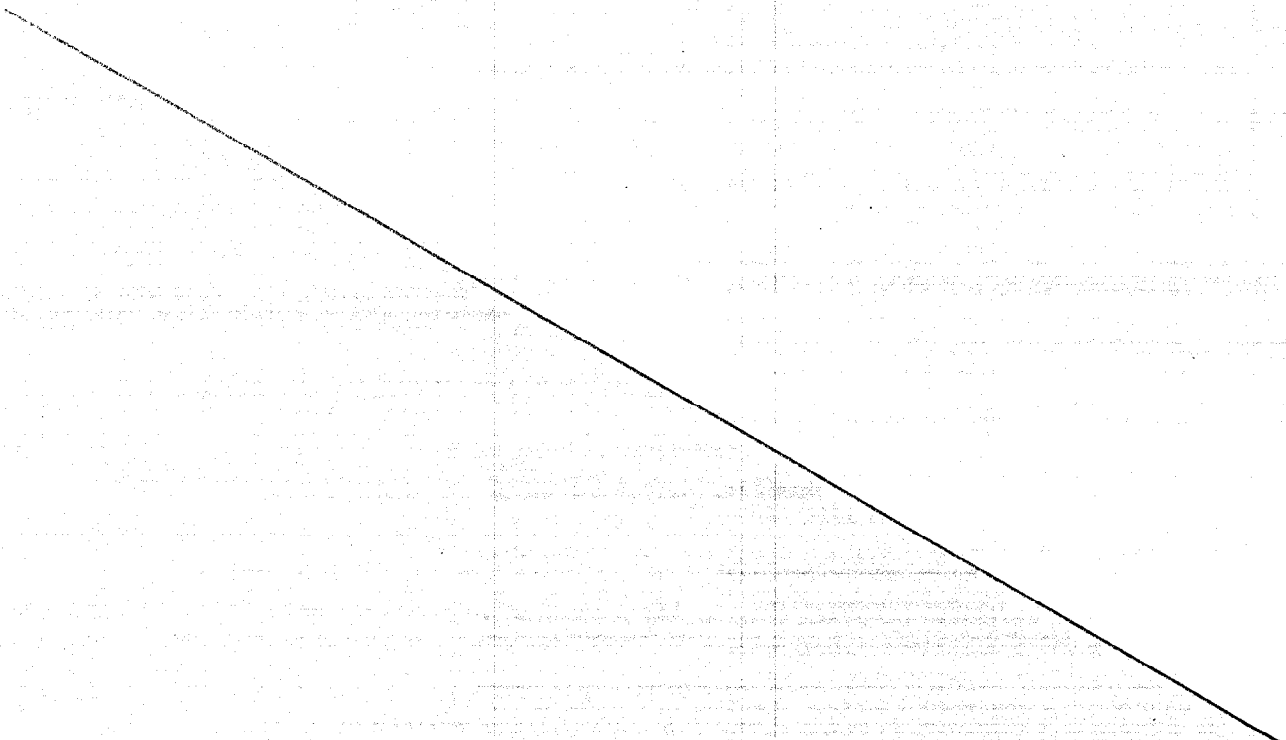
(c) The labeling of this product must include the following statements either on the outside container or wrapper of the retail package, under the “Other information” section of the Drug Facts labeling in accordance with § 201.66(c)(7), or in a package insert.

(1) “[Bullet] Studies have raised safety concerns that frequent use (more than once a day) of products containing nonoxynol 9 can increase vaginal

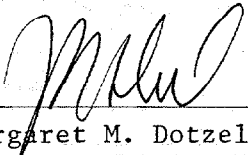
irritation, which may increase the risk of getting the AIDS virus (HIV) or other STDs from infected partners. Vaginal irritation may include symptoms such as burning, itching, or a rash, or you may not notice any symptoms at all. If you use these products frequently and/or have a new sex partner, multiple sex partners, or unprotected sex, see a doctor or other health professional for your best birth control and methods to prevent STDs.”

(2) “[Bullet] Correct use of a latex condom with every sexual act will help reduce the risk of getting the AIDS virus (HIV) and other STDs from infected partners.”

(d) Any drug product subject to this section that is not labeled as required and that is initially introduced or initially delivered for introduction into interstate commerce after [date 6 months after date of publication of the final rule in the **Federal Register**], is misbranded under section 502 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 352), is a new drug under section 505 of the act (21 U.S.C. 355), and is subject to regulatory action.



Dated: 12/19/02  
December 19, 2002.



Margaret M. Dotzel,  
Assistant Commissioner for Policy.

3 [FR Doc. <sup>03</sup>02-~~02~~???? Filed <sup>03</sup>??-??-02; 8:45 am]

BILLING CODE 4160-01-S

CERTIFIED TO BE A TRUE  
COPY OF THE ORIGINAL

